Claims 4, 10-12, 15 and 18 have been amended to correct claim dependency, and to better correspond to amended claim 1.

Finally, new claim 24 has been added. Claim 24 is drawn to a method according of claim 1 in which the target nucleotide is absent due to a mutation in the nucleic acid. This claim is supported at page 7, lines 15-18, as well as claim 18 as originally filed.

Attached is a marked-up copy of the amended claims, as well as a clean copy of the complete set of pending claims as amended. No new matter is introduced by those amendments.

Remarks

Claims 1-23 were considered in the office action of April 11, 2001. Claims 1-23 were rejected under 35 U.S.C. § 112, second paragraph. In addition, claims 1-23 were rejected under 35 U.S.C. § 103(a) over Haff et al., U.S. Patent No. 5,885,775 ("Haff"), in view of Mathies et al., U.S. Patent No. 5,869,225 ("Mathies").

Applicants thank the Examiner for the telephonic interview of June 20, 2001 during which the differences between instant invention and the prior art were discussed.

A. The Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-23 were rejected under 35 U.S.C § 112, second paragraph. Specifically, claims 1-23 were said to be indefinite in the recitation of "comprising a donor molecule" and "comprising an acceptor molecule" because, according to the office action, it was unclear where the donor and acceptor molecules were to be located. As amended, the claims recite "a primer having a covalently attached donor molecule", and a "dideoxy nucleotide having a covalently-attached acceptor molecule". As such, Applicants respectfully submit that the claims, as amended, clearly indicate the location of the acceptor and donor molecules.

Claims 2-23 were said to be indefinite in the recitation of "activates" in the context of a donor and acceptor interaction because the donor and acceptor lacked molecular characterization. As amended, the claims recite activation through fluorescent

energy transfer between defined donor and acceptor molecules (*i.e.*, a flourophore or a fluorescent dye, for which 'activation' produces a detectable fluorescent signal when the dideoxy nucleotide is incorporated into the primer extension product). This type of activation is taught by the specification at page 11, lines 12-30. Applicants respectfully submit that the claims, as amended, are unambiguous as the meaning of 'activation' with respect to the interaction between the claimed donor and the acceptor molecules.

Claims 20-23 were said to be indefinite in the recitation of a method of "identifying" a "single nucleotide polymorphic variant" in which, according to the office action, the identity of the variant must be known in order to perform the method. As amended, the claims now call for the determination of the presence of a target nucleotide that is located at a single nucleotide polymorphic locus. Applicants respectfully submit that this amendment resolves the concern presented in the office action.

For the reasons discussed above, Applicants respectfully submit that the rejections under U.S.C. § 112, second paragraph, should be reconsidered and withdrawn.

B. The Rejection under 35 U.S.C. § 103(a)

Claims 1-23 were rejected under 35 U.S.C. § 103(a) over Haff and Mathies. In order to establish *prima facie* obviousness under 35 U.S.C. § 103, the prior art references must teach or suggest all of the claim limitations. See e.g., In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Applicants' claims, as amended, recite methods for determining the presence of a target nucleotide on a nucleic acid using a primer that has a covalently-attached donor molecule. The acceptor molecule is covalently-attached to a dideoxy nucleotide which, if the target nucleotide is present on the nucleic acid, will be incorporated into a primer extension product and activated by fluorescent energy transfer from the donor molecules in accordance with Applicants' claimed invention.

Haff reports a method for primer extension, but entirely fails to disclose either a primer having a covalently-attached donor molecule, or a dideoxy nucleotide having a covalently-attached acceptor molecule, as recited by Applicants' claims.

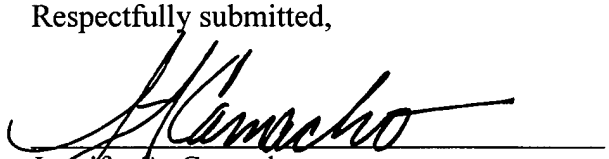
Mathies reports the use of fluorescent energy transfer methodology along with differentially labeled primers for allele detection. The labeled primers of Mathies comprise both an acceptor molecule and a donor molecule. Like Haff, Mathies entirely fails to report the use of a primer having a donor molecule and a separate dideoxy nucleotide having an acceptor molecule. In fact, Mathies emphasizes at column 5, lines 20-43 and at column 7, lines 16-21, the advantages of determining and maintaining a fixed degree of separation between the acceptor and donor molecules on a single backbone in each acceptor/donor pair in order to control the difference in mobility shift among conjointly used acceptor/donor pairs.

Because neither Haff not Mathies teach or suggest a primer comprising a donor molecules and a separate dideoxy nucleotide comprising an acceptor molecule, Haff and Mathies, even if combined, do not render Applicants' claims obvious. As such, Applicants respectfully submit that the rejection under U.S.C. § 103(a) should be reconsidered and withdrawn.

Conclusion

Applicants respectfully submit that the claims are in condition for allowance. If the Examiner believes that a conversation with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at the telephone number below.

Respectfully submitted,



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Amended Claims in Mark-Up Format

1. (Amended) A method for [identifying] determining the presence of a target nucleotide, the method comprising the steps of:

(a) exposing a biological sample to a nucleic acid primer capable of hybridizing with a nucleic acid, said primer having [and comprising] a covalently-attached donor molecule comprising a fluorophore or a fluorescent dye;

(b) performing a primer extension reaction in the presence of a dideoxynucleotide [nucleotide] complementary to the target nucleotide, said dideoxy nucleotide having a covalently-attached [and comprising an] acceptor molecule comprising a fluorophore or a fluorescent dye, said acceptor molecule being capable of [interacting with] being activated through fluorescent energy transfer from said donor molecule so as to produce a detectable fluorescent signal when said dideoxy nucleotide is incorporated into a product resulting from the primer extension reaction; [and]

(c) determining the presence of said fluorescent signal, said presence being indicative of incorporation of said dideoxy nucleotide into the primer extension product; and

(d) determining the presence of said target nucleotide as indicated by the incorporation of said dideoxy nucleotide into the primer extension product.

[identifying the target nucleotide incorporated into said primer as a function of said signal].

4. (Amended) The method of claim 1, wherein said extension reaction is performed in the presence of at least two different dideoxy nucleotides, each comprising a different acceptor molecule that produces a distinct fluorescent signal upon activation.

10. (Amended) The method of claim 1 [9], wherein said fluorescent dye is selected from the group consisting of 6-carboxyfluorescein (FAM), 6-carboxy-X-rhodamine (REG), N_1, N_1 N^1, N^1-tetramethyl-6-carboxyrhodamine (TAMARA), 6-carboxy-X-rhodomine (ROX), fluorescein, Cy5® or LightCycler-Red 640.

11. (Amended) The method of claim 1 wherein said donor molecule [further] comprises 6-carboxyfluorescein (FAM).

12. (Amended) The method of claim 11 wherein said acceptor molecule comprises [)], 6-carboxy-X-rhodomine (ROX).

15. (Amended) The method of claim 1 [13] wherein said [chain-terminating] dideoxy nucleotide is a 2'3 '-dideoxy nucleotide triphosphate[s] selected from the group consisting of ddATP, ddCTP, ddGTP, ddTTP and ddUTP.

18. (Amended) The method of claim 1, wherein said target nucleotide is present as a result of a nucleic acid mutation.

20. (Amended) The method of claim 4, wherein said target nucleotide is present at[A method for identifying] a single nucleotide polymorphic locus [variant, comprising the steps of:

exposing a sample to a first nucleic acid primer comprising a donor molecule, wherein said primer is capable of hybridizing to a nucleic acid in said sample at a locus immediately 5' to a single nucleotide polymorphic locus;

extending said primer in the presence of at least two nucleotides, each comprising a different acceptor molecule capable of interacting with said donor molecule to produce a detectable signal;

detecting said signal; and

identifying said one or more nucleic acids present at said polymorphic locus].

24. (New) The method of claim 1, wherein said target nucleotide is absent as a result of a nucleic acid mutation.